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Reproductive, menstrual, and medical risk factors for endometrial cancer: Results from a case-control study

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OBJECTIVE: Our objective was to evaluate the risk for endometrial cancer in relation to reproductive, menstrual, and medical factors.

STUDY DESIGN: A case-control study of 405 endometrial cancer cases and 297 population controls in five areas of the United States enabled risk to be evaluated.

RESULTS: A major risk factor was the absence of a prior pregnancy (relative risk 2.8, 95% confidence interval 1.7 to 4.6). The protective effect of pregnancy appeared to reflect the influence of term births, because spontaneous and induced abortions were unrelated to risk. Among nulliparous women infertility was a significant risk factor, with women having sought medical advice having nearly eight times the risk of those without difficulty conceiving. After adjustment for other reproductive characteristics, age at first birth and duration of breast-feeding were not related to risk.

CONCLUSIONS: Elevated risks were found for subjects reporting early ages at menarche (relative risk 2.4 for ages <12 vs ≥ 15) and longer days of flow (relative risk 1.9 for ≥ 7 vs <4 days), but there was no relationship with late ages at natural menopause. Height was not associated with risk, but there was a significant relation to weight, with the risk for 200 versus <125 pounds being 7.2 (95% confidence interval 3.9 to 13.3). After adjustment for weight and other factors, histories of hypertension and gallbladder disease were not significantly related to risk, but an effect of diabetes persisted (relative risk 2.0, 95% confidence interval 1.1 to 3.6). Hirsutism developing at older ages was also significantly related (relative risk 2.0, 95% confidence interval 1.2 to 3.4). (Am J Obstet Gynecol 1992;167:1317-25.)

Key words: Endometrial cancer, reproduction, menstruation, obesity, diabetes

In the last several decades there have been numerous studies addressing the effects of exogenous estrogens on the risk of endometrial cancer.[1, 2] Although relationships of different patterns of estrogen usage have now been well described, other epidemiologic characteristics of endometrial cancer remain less well clarified. In particular, questions remain as to the independence of various factors, because many of the identified risk factors appear to be correlated. For example, it is well known clinically that the woman at risk for developing the disease is "fat, forty, and infertile," but the relative importance of these factors has not been defined. Further, there are speculations that women with histories of diabetes, hypertension, gallbladder disease, and thyroid disease may experience elevated risks, but whether these effects are independent of the recognized association of endometrial cancer with obesity has yet to be resolved.

A variety of menstrual and reproductive characteristics have been shown to affect the risk of endometrial cancer, but the exact nature of these relationships is unclear. It is well known that multiparity is associated with reduced risk, but the role of miscarriages and spontaneous abortions has not been resolved. Further, the independence of effects of nulliparity and infertility and of age at menarche and menstrual irregularities have not been adequately addressed. The interrelationships between menstrual factors, reproductive factors, and weight are complex, with their respective roles in the pathogenesis of endometrial cancer being poorly understood.

To clarify the role of a variety of factors in the etiology of endometrial cancer, we undertook a multicenter study, enrolling a large number of newly diagnosed cases and matched population controls. Detailed information on a variety of relatively unexplored risk

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factors was collected, allowing a number of emerging hypotheses to be examined.

Material and methods

This case-control study was a collaborative effort with participating centers in five areas of the United States—Chicago, Illinois; Hershey, Pennsylvania; Irvine and Long Beach, California; Minneapolis, Minnesota; and Winston-Salem, North Carolina. Cases were accrued from seven hospitals in these areas during the period June 1, 1987, through May 15, 1990. Eligible for study were all patients with newly diagnosed cancer of the uterine corpus (hereafter referred to as endometrial cancer) who were between the ages of 20 to 74 years, resided in defined geographic catchment areas, and had not received previous treatment for their cancer. A total of 498 women were considered eligible for study.

For each eligible case we attempted to select one control matched for age (same 5-year group), race, and location of residence (this latter variable as an attempt to control for characteristics underlying referral of cases to the study hospitals). For patients <65 years old, controls were selected with random digit dialing techniques,[3] whereas older controls were selected with information provided by the Health Care Financing Administration.

Random digit dialing controls were selected by deriving a residential cluster matched for the telephone exchange of each eligible case. Telephone numbers were called, and an enumeration of female members aged 20 to 64 in each household was attempted. Of 15,820 telephone numbers sampled, 10,184 were assessed to be residential working numbers, and an enumeration of female members was obtained for 86%. Older controls were derived by randomly selecting from current Health Care Financing Administration computer tapes a subject of the same age, race, and zip code of residence as each eligible case. After the initial selection of subjects, a short telephone questionnaire was administered to determine whether the subjects had intact uteri. A total of 125 of the initially selected random digit dialing controls and 88 of the Health Care Financing Administration controls were eliminated because of their not being at risk for developing endometrial cancer. These subjects were replaced with other eligible subjects, so that there was an eventual accrual of 304 controls through random digit dialing techniques and 173 through Health Care Financing Administration files.

Interviewers trained in a standard manner conducted in-person interviews, usually in subjects' homes. Interviews lasted somewhat >1 hour (mean 76 minutes) and elicited detailed historic information on demographic factors, pregnancies, menstruation and menopause, contraceptive behavior, use of exogenous hormones, diet, alcohol intake, body size changes, smoking, medical conditions, and family history of cancer. Interviews were completed with 434 of 498 eligible cases (87.1%) and with 313 of 477 eligible controls (65.6%). Eligible subjects who could not be interviewed were not replaced. The reasons for nonresponse were refusals (4.8% of cases vs 21.8% of controls), illness (1.0% vs 2.3%), death (1.0% vs 1.0%), communication problems (3.6% vs 2.5%), relocation of subjects or inability to locate them (0.2% vs 3.1%), and other problems (0.2% vs 3.6%). In addition, physician consent for interview was denied for 2.0% of the cases. The response rate was considerably higher for the random digit dialing than the Health Care Financing Administration controls (76.3% vs 46.8%), primarily because of a lower refusal rate among the younger subjects (16.8% vs 30.6%).

All cases were confirmed by pathologic examination, with 93% of the interviewed cases having a classification of epithelial cancer. Because of the distinctive epidemiologic characteristics of sarcomas,[4] this analysis focused on interviews with the 405 epithelial cancer cases and their 297 matched controls.

To estimate the risk of endometrial cancer associated with various factors, we calculated odds ratios as approximations of relative risks. Unconditional logistic regression was used to adjust for potential confounding variables, with maximum likelihood estimates of relative risks and 95% confidence intervals derived.[5] The exclusion of 1.0 from this confidence interval indicated that the associated relative risk was statistically significant at $p < 0.05$. The risk factors that were most correlated with other exposures of interest, and therefore potential confounders, were education, number of births, weight, and exogenous hormone use. A generalized model incorporating these variables (in addition to age) was used to evaluate the role of other potential risk factors. When it was necessary to adjust for other potential confounders, models were expanded to incorporate these additional variables. Tests for trends in the logistic analyses were obtained by categorizing the exposure variable and treating the scored variables as continuous, after unknown values were eliminated.

Results

The mean age of the cases at interview was 59.2 years, compared with 58.0 years among the controls. Cases and controls were comparable in regard to race, with the majority classifying themselves as non-Hispanic white (Table I). Although cases were more educated than were controls, there were no significant differences between the two study groups according to reported family income. Cases reported less frequent use of oral contraceptives than did controls (use for ≥ 5 years 5.2%

vs 11.8%, respectively), whereas estrogen use was more frequent among cases (use for ≥5 years 12.3% vs 3.7%, respectively).

Risks associated with different reproductive events are shown in Table II. Cases were much more likely than controls to have never been pregnant (age-adjusted relative risk 2.8, 95% confidence interval 1.7 to 4.6). Among gravid women there was a significant linear trend of decreasing risk with increasing numbers of pregnancies. This relationship, however, was entirely attributable to effects of numbers of live births or stillbirths, because induced abortions and miscarriages were not independent predictors of risk. Histories of a prior live birth and stillbirth were associated with similar reductions in risk, and after adjustment for other pertinent risk factors women with one or more term births had a relative risk of 0.4 (95% confidence interval 0.2 to 0.6) compared with women with no prior births. In addition, there was a significant trend of decreasing risk with number of births (p for trend <0.001). After the number of births was controlled, there was no relationship of risk with age at which the first birth occurred. Ever having breast-fed an infant was not associated with risk, nor was total duration of breast-feeding.

To assess the extent to which nulliparity effects were explained by infertility, we evaluated risk in relation to whether the patient reported ever having had difficulty conceiving (attempting to get pregnant for at least two consecutive years without success) and whether advice had ever been sought for infertility. Histories of either of these occurrences were not strongly associated with risk (respective relative risks of 1.2 and 1.1). However, when we examined histories of infertility according to parity status (Table III), we found that among married, nulliparous women both difficulty conceiving and having sought medical advice for infertility were risk factors. Thus among this subgroup difficulty conceiving was associated with a relative risk of 1.8 (95% confidence interval 0.4 to 7.6), whereas a medical workup for infertility was associated with a significant 7.6-fold increased risk (95% confidence interval 1.4 to 40.2). Never-pregnant and never-married women were at a slightly elevated risk relative to nulliparous women without difficulty conceiving, presumably because this group of unmarried women comprised both fertile and infertile women. We attempted to assess whether the excess risk associated with medical workups for infertility could be attributed to any specific cause of infertility, but many women were unable to provide this information and there were few women within any one cause of infertility grouping.

Relationships with reported anthropometric variables revealed no linear relationship of risk with height (Table IV). Weight was a strong predictor of risk, although substantially elevated risks were restricted to the highest extremes of weight. Subjects reporting a prediagnostic weight of ≥200 pounds had more than seven times the risk of those weighing <125 pounds, whereas the risk was elevated nearly ninefold among the small group weighing ≥225 pounds (data not shown). Examination of Quetelet's index (weight ÷ height^2) showed increases in risk for subjects with higher body masses, although effects with this variable were of somewhat lesser magnitude than weight alone. Thus subjects with Quetelet's index ≥32 were at a fourfold excess risk, whereas the risk rose to 6.0 among the limited number of subjects with an index of ≥35.

Age at menarche was inversely associated with risk, with those reporting onset before age 12 having approximately twice the risk as those whose periods began at age ≥15 (Table V). This relationship was unaffected by further adjustment for a history of infertility or for weight at young ages (i.e., immediately before and after adolescence). Risk did not vary by histories of amenorrhea or by usual regularity of the menstrual cycle, although more cases than controls could not recall when their cycles became regular (data not shown). However, risk was elevated among women with longer days of flow, an association that persisted after adjustment for age at menarche. Subjects were also questioned about various physical changes associated with

Table I. Distribution of endometrial cancer cases and controls by selected demographic factors

	Cases		*Controls*	
	No.	*%*	*No.*	*%*
Age (yr)				
<45	39	9.6	34	11.4
45-54	78	19.3	70	23.6
55-64	146	36.0	109	36.7
≥65	142	35.1	84	28.3
Race				
White, non-Hispanic	360	88.9	269	90.6
White, Hispanic	10	2.5	9	3.0
Black, non-Hispanic	23	5.7	16	5.4
Other	7	1.7	3	1.0
Unknown	5	1.2	0	—
Education (yr)				
<12	84	20.7	76	25.6
12	123	30.4	91	30.6
13 to 15	63	15.6	60	20.2
≥16	128	31.6	67	22.6
Other	1	0.2	3	1.0
Unknown	6	1.5	0	—
Family income				
<$10,000	65	16.0	43	14.5
$10,000 to $29,999	119	29.4	110	37.0
$30,000 to $49,999	108	26.7	65	21.9
$50,000 to $69,999	33	8.1	27	9.1
≥$70,000	53	13.1	35	11.8
Unknown	27	6.7	17	5.7

Table II. Relative risks of endometrial cancer by reproductive factors

	No. of cases	*No. of controls*	*Relative risk**	*Relative risk†*	*95% Confidence interval*
Ever pregnant					
Yes	328	273	1.00		
No	77	24	2.79		
No. of term births					
0	90	28	1.00	1.00	
1	66	31	0.63	0.55	0.3-1.1
2	86	87	0.31	0.32	0.2-0.6
3	71	57	0.37	0.42	0.2-0.8
4	49	35	0.41	0.54	0.3-1.0
≥5	43	59	0.21	0.22	0.1-0.4
Trend test				$p < 0.001$	
No. of miscarriages					
0	317	218	1.00	1.00‡	
1	62	55	0.76	0.99	0.6-1.6
≥2	26	24	0.72	1.09	0.6-2.1
Trend test				$p = 0.84$	
Ever had an induced abortion					
No	383	279	1.00	1.00‡	
Yes	22	18	0.94	1.00	0.5-2.0
Ever breast-fed§					
No	83	67	1.00	1.00‡	
Yes	190	169	0.87	1.01	0.6-1.6

*Adjusted for age at interview.

†Adjusted for age at interview, years of education, recent weight, oral contraceptive use, and menopausal estrogen use.

‡Adjusted additionally for number of births.

§Excludes women with no live births.

Table III. Relative risks of endometrial cancer by parity and histories of difficulty conceiving or having sought medical advice for infertility

	No. of cases	*No. of controls*	*Relative risk**	*95% Confidence interval*
Nulliparous, no difficulty	21	12	1.00	
Nulliparous, no advice sought	14	4	1.82	0.4-7.6
Nulliparous, advice sought	21	2	7.57	1.4-40.2
Parous, no difficulty	272	234	0.65	0.3-1.5
Parous, no advice sought	19	12	0.97	0.3-3.0
Parous, advice sought	24	23	0.52	0.2-1.4
Never married and never pregnant	34	10	1.46	0.5-4.3

*Adjusted for age at interview, years of education, recent weight, oral contraceptive use, and menopausal estrogen use.

menstruation, including weight gain, breast tenderness, severe headaches, severe cramps, marked irritability, and back pain, but none of these were associated with any substantial alterations in risk.

The majority of subjects were menopausal, with most having undergone a natural menopause. Naturally menopausal women had a risk similar to that of premenopausal subjects (relative risk 1.1). Among the naturally menopausal women there was no evidence of a relationship of risk with age at menopause. Adjustment for additional variables, including age at menarche or smoking, did not alter the effect. The absence of an association persisted even when analyses were restricted to low-risk subgroups (e.g., thin women, smokers, and nonusers of estrogen).

When subjects were questioned regarding physician-diagnosed diseases that developed at least 1 year before diagnosis (or equivalent period for controls) (Table VI), excess age-adjusted risks were associated with histories of diabetes (relative risk 2.2), gallbladder disease (relative risk 1.8), and endometriosis (relative risk 2.1). The association with gallbladder disease, however, did not persist after adjustment for other factors, notably weight (relative risk 1.4, 95% confidence interval 0.8 to 2.3). The increased risk associated with diabetes remained significant after adjustment (relative risk 2.0, 95% confidence interval 1.1 to 3.6), even when weight was adjusted for as a continuous variable. In addition, the association remained when only diseases diagnosed >5 years before diagnosis were considered (relative risk 2.1, 95% confidence interval 0.9 to 4.7). The majority of subjects (70%) reported non–insulin-dependent diabe-

Table IV. Relative risks of endometrial cancer by height, weight, and body mass index

	No. of cases	*No. of controls*	*Relative risk**	*95% Confidence interval*
Height (in)				
<62	61	50	1.00	
62-63	107	76	1.18	0.7-2.0
64-65	120	86	1.18	0.7-1.9
66-67	77	55	1.31	0.8-2.3
≥68	35	26	1.20	0.6-2.4
Unknown	5	4	0.64	0.1-3.6
Trend test			$p = 0.48$	
Weight (lb)				
<125	62	56	1.00	
125-149	102	98	1.12	0.7-1.8
150-174	63	78	0.91	0.5-1.6
175-199	56	37	1.94	1.1-3.5
≥200	117	27	7.18	3.9-13.3
Unknown	5	1	1.87	0.1-26.1
Trend test			$p < 0.001$	
Body mass index†				
<23	96	87	1.00	
23-25	63	82	0.82	0.5-1.3
26-28	46	52	0.88	0.5-1.5
29-31	60	24	2.70	1.5-4.9
≥32	135	47	4.15	2.5-6.8
Unknown	5	5	0.59	0.1-3.2
Trend test			$p < 0.001$	

*Adjusted for age at interview, years of education, number of births, oral contraceptive use, and menopausal estrogen use.
†Quetelet's index: Weight (kilograms)/Height (meters)^2.

tes, which was associated with a slightly higher risk (relative risk 2.1, 95% confidence interval 1.0 to 4.2) than insulin-dependent diabetes (relative risk 1.7, 95% confidence interval 0.6 to 4.6). The positive association of risk with a prior diagnosis of endometriosis became stronger after adjustment for parity but nonetheless remained nonsignificant (relative risk 2.9, 95% confidence interval 0.5 to 7.3). Other diseases, including hypertension, thyroid disease, arthritis, blood clots, and liver disease were not associated with any substantial alterations in the risk of endometrial cancer. A history of having been diagnosed with high cholesterol levels was associated with a significant reduction in risk (relative risk 0.6, 95% confidence interval 0.4 to 0.9). Histories of pelvic inflammatory disease and polycystic ovaries were both associated with substantially reduced risks, but the numbers of women involved were small and neither of the associations were statistically significant.

Subjects were also questioned regarding two conditions not necessarily diagnosed by a physician, namely the occurrence of excess facial hair (to the extent that removal was considered) and acne that appeared to be of a greater degree than that experienced by their peers. A problem with excess facial hair was associated with a significant 2.0-fold excess risk (95% confidence interval 1.2 to 3.4) with the elevations in risk entirely attributable to problems arising when subjects were ≥40 years old. In contrast, self-diagnosed problems with acne were not associated with an excess risk (relative risk 1.0).

A total of 19 cases and 20 controls reported a personal history of cancer other than nonmelanotic skin cancer, with breast cancer having affected two cases versus eight controls. A history of cancer in a first-degree relative generally was not associated with an excess risk for endometrial cancer (relative risk 0.8), although more cases than controls (five versus one) reported a first-degree female relative with endometrial cancer.

Because of the use of different controls for younger versus older subjects and the possibility of variations in risk patterns according to age at diagnosis of endometrial cancer, we examined risk factors separately for subjects under and over age 65 (Table VII). This analysis showed similar patterns of risk across the two age groups, with the exception of a history of infertility, which was a risk factor among the younger subjects and an apparent protective factor among the older women. The magnitude of risk associated with a number of factors was higher among the older subjects, although the fewer number of subjects involved led to greater instability of the estimates.

Comment

Similar to a number of other investigations, this study confirmed that nulligravidity is a major risk factor for endometrial cancer,[6-10] with the absence of a previous

Table V. Relative risks of endometrial cancer by menstrual characteristics

	No. of cases	*No. of controls*	*Relative risk**	*95% Confidence interval*
Age at menarche (yr)				
≥15	34	41	1.00	
14	55	47	1.60	0.8-3.1
13	111	90	1.37	0.8-2.5
12	116	74	1.79	0.9-3.3
<12	88	43	2.41	1.2-4.7
Unknown	1	2	1.88	0.1-23.1
Trend test			$p = 0.01$	
Days of flow				
1-3	55	57	1.00	
4-6	281	203	1.47	0.9-2.4
≥7	67	36	1.90	1.0-3.6
Unknown	2	1	1.10	0.1-17.7
Trend test			$p = 0.04$	
Type of menopause				
Premenopausal	96	83	1.00	
Natural menopause	300	207	1.10	0.6-2.0
Other	3	7	0.29	0.1-1.3
Unknown	6	0		
Age at menopause†				
<45	39	28	1.00	
45-49	89	69	0.88	0.5-1.7
50-54	133	83	0.99	0.5-1.8
≥55	36	27	0.77	0.4-1.7
Unknown	3	0		
Trend test			$p = 0.74$	

*Adjusted for age at interview, years of education, number of births, recent weight, oral contraceptive use, and menopausal estrogen use.

†Restricted to naturally menopausal women.

Table VI. Relative risks of endometrial cancer by selected medical diagnoses

	No. of cases	*No. of controls*	*Relative risk**	*Relative risk†*	*95% Confidence interval*
Hypertension	154	101	1.16	0.94	0.6-1.4
Diabetes	58	21	2.18	1.95	1.1-3.6
Gallbladder disease	78	35	1.77	1.41	0.8-2.3
Thyroid disease	77	44	1.35	0.98	0.6-1.5
Arthritis	127	100	0.87	0.70	0.5-1.0
High cholesterol	59	65	0.58	0.56	0.4-0.9
Blood clots	25	16	1.13	1.04	0.5-2.1
Liver disease	9	5	1.33	1.55	0.4-5.4
Endometriosis	5	2	2.14	2.92	0.5-7.3
Pelvic inflammatory disease	9	13	0.55	0.56	0.2-1.5
Polycystic ovaries	2	6	0.26	0.30	0.0-1.7

*Adjusted for age at interview. Unknowns were included in analysis but are not presented in table.

†Adjusted for age at interview, years of education, number of births, recent weight, oral contraceptive use, and menopausal estrogen use.

pregnancy being associated with a nearly threefold elevation in risk. The protective effect of pregnancy appeared to be dependent on the pregnancy being carried to term, because prior miscarriages and induced abortions had no independent effects. The occurrence of one or more births was associated with about a 60% decrease in risk compared with no prior births, with risk decreasing somewhat further with additional births. Unlike the relationship with breast cancer, the age at which a woman first gave birth did not appear related to risk. In addition, in accordance with other study results, breast-feeding did not appear to alter the risk of endometrial cancer.[6, 11, 12]

Studies showing higher endometrial cancer risks for married nulliparous women than for unmarried women suggest that infertility may play an etiologic role.[6, 11] Few studies, however, have specifically examined infertility in relation to risk for endometrial cancer. One study noted a nonsignificant elevation in risk,[10] whereas another noted a relative risk of 3.5 for women who reported an inability to achieve pregnancy for ≥3 years.[7] Our study highlighted the difficulties in assess-

Table VII. Endometrial cancer risk factors by age at onset of disease*

	Subjects aged <65 yr			*Subjects aged ≥65 yr*		
	No. of cases	*Relative risk*	*95% Confidence interval*	*No. of cases*	*Relative risk*	*95% Confidence interval*
Education (yr)						
<12	46	1.00		38	1.00	
12	86	1.54	0.8-2.8	37	1.33	0.6-3.1
13-15	40	1.05	0.5-2.1	23	2.24	0.8-6.2
≥16	88	2.25	1.2-4.4	40	2.63	0.9-7.0
No. of births						
0	61	1.00		29	1.00	
1	33	0.45	0.2-1.2	33	0.54	0.1-2.1
2	62	0.37	0.2-0.9	24	0.14	0.0-0.5
3	44	0.40	0.2-0.9	27	0.35	0.1-1.3
≥4	63	0.33	0.1-0.8	29	0.16	0.0-0.6
Previous infertility						
No	199	1.00		127	1.00	
Yes, no advice sought	36	1.94	0.9-4.0	9	0.41	0.1-1.2
Yes, advice sought	28	1.45	0.4-5.1	6	0.20	0.0-1.4
Weight (lb)						
<150	104	1.00		60	1.00	
150-174	35	0.67	0.4-1.2	28	0.93	0.4-2.1
175-199	37	1.43	0.8-2.6	19	2.30	0.7-7.1
≥200	85	5.05	2.7-9.5	32	4.35	1.6-12.2
Age at menarche (yr)						
≥14	47	1.00		42	1.00	
13	75	1.10	0.6-2.0	36	1.15	0.5-2.6
12	77	1.34	0.7-2.4	39	1.51	0.7-3.5
<12	63	1.65	0.9-3.1	25	4.34	1.2-15.8
Previous diabetes						
No	225	1.00		116	1.00	
Yes	36	2.31	1.0-5.3	22	2.03	0.8-5.4

*Relative risks adjusted for all variables shown. In addition, risks among younger subjects adjusted for oral contraceptive use and among older subjects for menopausal estrogen use. Subjects with unknown values were included in models but associated risks are not presented.

ing the association, because infertility emerged as a risk factor only when examined in relation to parity. Among nulliparous women, difficulty conceiving or ever having sought advice for infertility were associated with relative risks of 1.8 and 7.6, respectively. Although we attempted to examine risk according to causes of infertility, we were limited by nonspecific information. However, other studies, which have found elevated endometrial cancer risks associated with both anovulation[13] and progesterone deficiencies,[14, 15] support an effect of unopposed estrogens on the development of endometrial cancer.

Although most studies that have related early ages at menarche to an increased risk of endometrial cancer have found associations to be rather weak and trends inconsistent,[6, 7, 10, 11] our investigation found age at menarche to have a significant effect on risk. In previous investigations it has been unclear to what extent relationships reflected increased exposure to ovarian hormones or other correlates of early menarche. Thus it is noteworthy that the strong associations that we observed with age at menarche persisted after adjustment for a variety of risk factors, including weight and parity.

Because early menarche has been found to reflect early onset of regular periods and thus longer exposure to circulating hormones, it was of interest to examine endometrial cancer risk in relation to histories of menstrual irregularities. Amenorrhea leading to physician consultation has been associated with a substantial excess risk of endometrial cancer in young women.[7] Furthermore, Wynder et al.[12] noted an association between endometrial cancer risk and both heavy menstrual bleeding and premenstrual breast swelling. We failed to find any relationship of risk to either regularity of menstrual cycles or histories of amenorrhea, but subjects reporting longer days of flow were at a significant excess risk. Although subjects were asked to provide information on usual menstrual characteristics, the association with menstrual flow might merely reflect recall of prediagnostic symptoms. Alternatively, the effect could be a consequence of the endogenous hormonal abnormalities that frequently accompany menorrhagia.

Dissimilar to a number of studies,[6, 11, 12] we did not find that endometrial cancer was associated with late age at natural menopause, an effect that has been hypothesized to reflect prolonged exposure of the uterus to estrogen stimulation in the presence of an-

ovulatory (progesterone-deficient) cycles.[13] We thought initially that the absence of association in our data might reflect confounding by other factors, including exogenous hormone use, but adjustment for a variety of other risk factors did not alter effects. Further, effects of age at menopause were not apparent in any subgroups examined, including women without other risk factors (e.g., exogenous hormones, obesity). This failure to find a relationship of risk with age at menopause may reflect the difficulties in distinguishing natural cessation of menopause from abnormal bleeding preceding the diagnosis of endometrial cancer, especially among older women.

Similar to a number of other investigations,[6, 7, 11-16] we found weight to be strongly related to endometrial cancer risk. Relationships were stronger with weight than for measures of obesity, such as Quetelet's index. Of interest was the finding that very heavy women (notably those weighing >200 pounds) had a disproportionately high risk, a finding consistent with several other investigations.[7, 12] It is well recognized that adipose tissue is the primary site in postmenopausal women for conversion of adrenal androstenedione to estrone. Obesity has also been related to lower levels of sex hormone–binding globulin, leading to greater bioavailability of estrogens.[17] In premenopausal women obesity may increase risk through more frequent anovulatory cycles, leading to lower levels of progesterone. Several recent studies indicate that endometrial cancer risk might vary not only by the amount of body fat but also by its distribution,[18-21] an issue that deserves further research.

Several studies have noted elevated risks of endometrial cancer associated with previous diagnoses of diabetes, hypertension, thyroid disease, and gallbladder disease, but most have not investigated the extent to which associations might have reflected confounding by weight or surveillance bias. Elwood et al.[6] found that associations with both diabetes and hypertension persisted after adjustment for weight and socioeconomic status, although relationships were restricted to recent diagnoses, suggesting detection bias. In our study we found no relationship of risk to hypertension, consistent with an investigation in China.[22] However, a history of diabetes was associated with a significant twofold excess in risk, which persisted over time and was independent of effects of weight. This finding, in conjunction with indications that diabetic women have elevated levels of lipids, estrogens, and possibly other hormones,[23] highlights the need for further study of endometrial cancer risk among diabetics. Furthermore, our data suggested an increased risk among women reporting histories of hirsutism. Although we are not aware of other studies that have examined this factor in relation to endometrial cancer risk, an association would appear plausible, given recognized endogenous hormonal influences on the development of hirsutism.[24, 25]

Our results, in agreement with previous studies, support a central role for hormones in the etiology of endometrial cancer. Use of unopposed estrogens greatly enhanced risk, whereas oral contraceptive use resulted in substantially reduced risks, presumably reflecting the antiestrogenic effects of progestins. Further implicating a role for hormones were substantially elevated risks among obese women, who have been found to have greater conversion rates and bioavailability of estrogens. Although the biologic mechanisms underlying the effects of nulliparity (early age at menarche, extended days of menstrual flow, history of diabetes, and hirsutism developing at older ages) remain less clear, it is possible that they may also operate through hormonal mechanisms, leading to a unifying scheme as the etiology of this disease.

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